

ANSWER 1 MARPAT COPYRIGHT 2003 ACS

AN 134:242656 MARPAT

TI Phospholipid prodrugs of anti-proliferative drugs

IN Kozak, Alexander; Shapiro, Israel; Vinnikova, Marina; Ershov, Leonid; Senderikhin, Alexander; Ayalon, Oran

PA D-Pharm Limited, Israel

SO PCT Int. Appl., 51 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001019320	A2	20010322	WO 2000-IL562	20000913
	WO 2001019320	A3	20010927		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000073093	A5	20010417	AU 2000-73093	20000913
	EP 1218013	A2	20020703	EP 2000-960946	20000913
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	JP 2003514770	T2	20030422	JP 2001-522958	20000913
PRAI	IL 1999-131887	19990914			
	WO 2000-IL562	20000913			
AB	The invention discloses prodrugs comprising anti-proliferative drugs covalently linked, via a bridging group, to a phospholipid moiety such that the active species is preferentially released, preferably by enzymic cleavage, at the required site of action. The invention further discloses pharmaceutical compns. comprising said prodrugs and the uses thereof for the treatment of diseases and disorders related to inflammatory, to degenerative or atrophic conditions, and to uncontrolled cell growth. A methotrexate deriv. 1-stearoyl-2-[3-(.alpha.-dodecylate-.gamma.-methotrexate-amido)-propanoyl]-sn-glycero-3-phosphatidylcholine was prepd., and examd. for its inhibitory effect on human leukemia cell growth.				
ST	cell growth inhibitor phospholipid deriv prepn; methotrexate antitumor phospholipid deriv prodrug prepn				
IT	Antitumor agents (Burkitt's lymphoma; phospholipid prodrugs of anti-proliferative drugs)				
IT	Nervous system (Huntington's chorea, treatment of; phospholipid prodrugs of anti-proliferative drugs)				
IT	Mental disorder (Pick's disease, treatment of; phospholipid prodrugs of anti-proliferative drugs)				
IT	Drug delivery systems (aerosols; phospholipid prodrugs of anti-proliferative drugs)				
IT	Nervous system (amyotrophic lateral sclerosis, treatment of; phospholipid prodrugs of anti-proliferative drugs)				
IT	Antitumor agents (bladder; phospholipid prodrugs of anti-proliferative drugs)				
IT	Drug delivery systems				

(capsules; phospholipid prodrugs of anti-proliferative drugs)

IT Brain, disease
(cerebrovascular, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Uterus, neoplasm
(cervix, inhibitors; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(cervix; phospholipid prodrugs of anti-proliferative drugs)

IT Chorion
(choriocarcinoma, inhibitors; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(choriocarcinoma; phospholipid prodrugs of anti-proliferative drugs)

IT Intestine, neoplasm
(colon, inhibitors; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(colon; phospholipid prodrugs of anti-proliferative drugs)

IT Nervous system
(degeneration, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Mental disorder
(dementia, multi-infarct, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Mental disorder
(dementia, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Mental disorder
(dementia, vascular, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Nerve, disease
(diabetic neuropathy, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Nervous system
(disease, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Mycosis
(fungoides, inhibitors; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
(gels; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(head; phospholipid prodrugs of anti-proliferative drugs)

IT Liver, neoplasm
(hepatoma, inhibitors; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(hepatoma; phospholipid prodrugs of anti-proliferative drugs)

IT Neoplasm
(hydatidiform mole, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Intestine, disease
(inflammatory bowel syndromes, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Intestine, neoplasm
Lung, neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Skin, neoplasm
(inhibitors; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
(injections, i.v.; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(intestine; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents

(lung; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(lymphocytic leukemia; phospholipid prodrugs of anti-proliferative drugs)

IT Eye, disease
(macula, degeneration, age-related, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(mammary gland; phospholipid prodrugs of anti-proliferative drugs)

IT Headache
(migraine, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Skin, neoplasm
(mycosis fungoides, inhibitors; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(mycosis fungoides; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(myelogenous leukemia; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
(nasal; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(neck; phospholipid prodrugs of anti-proliferative drugs)

IT Bladder

Head

Mammary gland

Neck, anatomical

Prostate gland

Urinary tract
(neoplasm, inhibitors; phospholipid prodrugs of anti-proliferative drugs)

IT Trophoblast
(neoplasm, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(non-Hodgkin's lymphoma; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
(ointments; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
(ophthalmic; phospholipid prodrugs of anti-proliferative drugs)

IT Nerve
(optic, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
(oral; phospholipid prodrugs of anti-proliferative drugs)

IT Pharynx
(oropharynx carcinoma, inhibitors; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(oropharynx carcinoma; phospholipid prodrugs of anti-proliferative drugs)

IT Bone, neoplasm
(osteosarcoma, inhibitors; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(osteosarcoma; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(ovary; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
(pancreas; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
(parenterals; phospholipid prodrugs of anti-proliferative drugs)

IT Anti-Alzheimer's agents
Anti-inflammatory agents
Antiarthritis
Antiasthmatics
Antiparkinsonian agents
Antirheumatic agents
Antitumor agents
 (phospholipid prodrugs of anti-proliferative drugs)

IT Lysophosphatidylcholines
RL: RCT (Reactant); RACT (Reactant or reagent)
 (prepn. of phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
 (prodrugs; phospholipid prodrugs of anti-proliferative drugs)

IT Proliferation inhibition
 (proliferation inhibitors; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
 (prostate gland; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
 (rectal; phospholipid prodrugs of anti-proliferative drugs)

IT Connective tissue
 (scleroderma, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
 (skin; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
 (solns.; phospholipid prodrugs of anti-proliferative drugs)

IT Brain, disease
 (stroke, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
 (suppositories; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
 (susensions; phospholipid prodrugs of anti-proliferative drugs)

IT Lupus erythematosus
 (systemic, treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
 (tablets; phospholipid prodrugs of anti-proliferative drugs)

IT Drug delivery systems
 (topical; phospholipid prodrugs of anti-proliferative drugs)

IT Granulomatous disease
Multiple sclerosis
Psoriasis
 (treatment of; phospholipid prodrugs of anti-proliferative drugs)

IT Antitumor agents
 (urinary tract; phospholipid prodrugs of anti-proliferative drugs)

IT 9001-84-7, Phospholipase A2 9013-93-8, Phospholipase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (activated by; phospholipid prodrugs of anti-proliferative drugs)

IT 330658-48-5P 330658-49-6P 330658-50-9P 330658-51-0P 330658-52-1P
330658-55-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of phospholipid prodrugs of anti-proliferative drugs)

IT 330658-53-2 330658-54-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (prepn. of phospholipid prodrugs of anti-proliferative drugs)

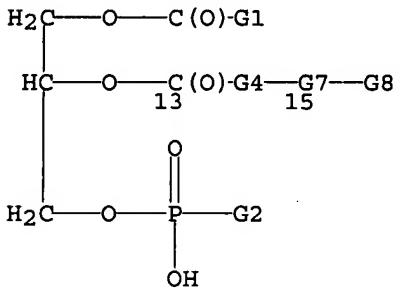
IT 50-91-9, 5-Fluoro-2'-deoxyuridine 56-12-2, 4-Aminobutanoic acid, reactions 59-05-2, Methotrexate 60-32-2, 6-Aminohexanoic acid 64-19-7, Acetic acid, reactions 76-83-5, Trityl chloride 107-95-9,

3-Aminopropanoic acid 123-76-2, Levulinic acid 501-53-1, Benzyl chloroformate 660-88-8, 5-Aminovaleric acid 1002-57-9, 8-Aminooctanoic acid 1069-66-5, Sodium 2-Propylpentanoate 4160-82-1,
 3,3-Dimethylglutaric anhydride 19420-57-6
 RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of phospholipid prodrugs of anti-proliferative drugs)

IT 1947-00-8P, 6-[N-(Benzylloxycarbonyl)amino]hexanoic acid 2304-94-1P
 5066-71-7P 5105-78-2P 10343-71-2P 23135-50-4P 23434-40-4P
 57444-77-6P 76523-73-4P 93349-30-5P 112489-84-6P 163225-49-8P
 271781-53-4P 330658-56-5P 330658-57-6P 330658-58-7P 330658-59-8P
 330658-60-1P 330658-62-3P 330658-64-5P 330658-66-7P 330658-68-9P
 330658-69-0P 330658-70-3P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (prepn. of phospholipid prodrugs of anti-proliferative drugs)

MSTR 1

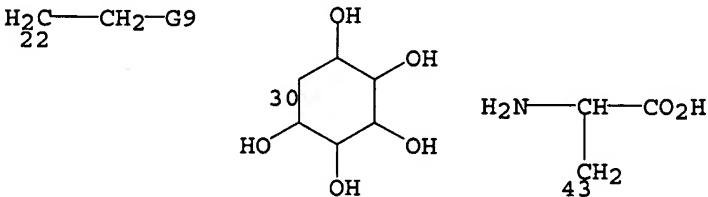


G1 = Ak<EC (2-30) C, BD (0-) D (0-) T> (SO) /
 (SC heptadecyl)

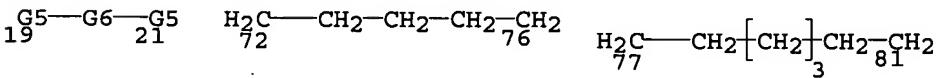
G2 = OH / 16

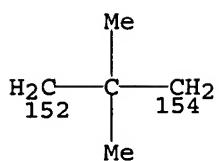


G3 = R<TX "phospholipid head group"> / (SC 22 / 30 / 43)

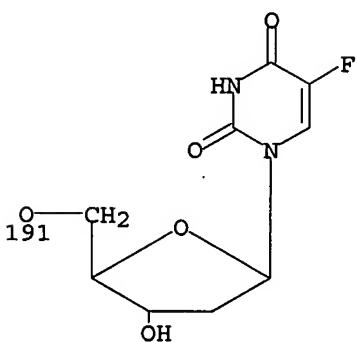
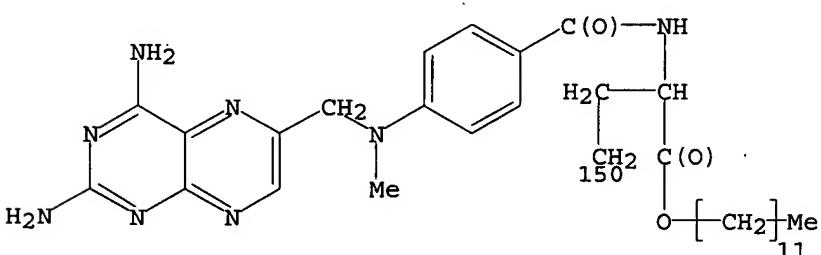
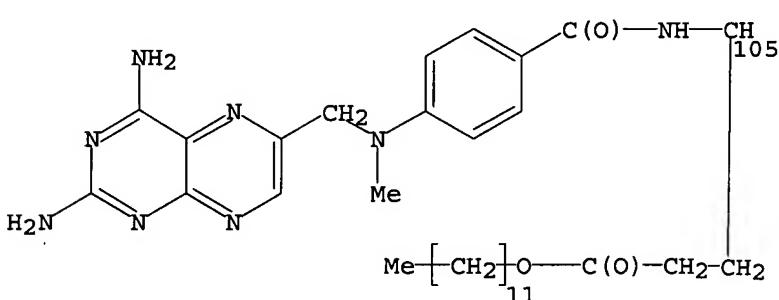
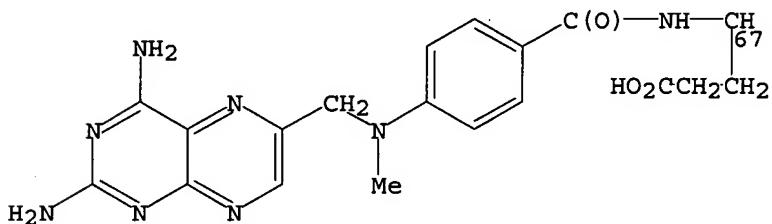


G4 = Ak<EC (2-15) C, BD (0-) D (0-) T> (SO) /
 Cb<EC (3-15) C, BD (0-) D (0-) T> (SO) / 19-13 21-15 /
 Hy<EC (3-) A (1-) Q (0-) O (0-) S (0) OTHERQ,
 BD (0-) D (0-) T> (SO) / (SC CH₂CH₂ / CH₂CH₂CH₂ /
 72-13 76-15 / 77-13 81-15 / 152-13 154-15)

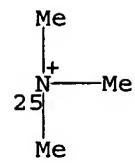




G5 = Ak<EC (1-) C, BD (0-) D (0-) T> (SO)
 G6 = O / S
 G7 = NULL / O / S / NH (SO) / C(O)
 G8 = R<TX "residue of anti-proliferative drug"> /
 (SC 67 / 105 / 150 / 191)



G9 = NH₂ / 25



MPL: claim 1

NTE: or pharmaceutically acceptable salts

NTE: additional oxygen or sulfur atom interruptions in G4 aliphatic chains
also claimed

=> d his

(FILE 'HOME' ENTERED AT 15:44:20 ON 29 MAY 2003)

FILE 'REGISTRY' ENTERED AT 15:44:29 ON 29 MAY 2003

L1 0 S STEAROYL DODECYLATE MTX AMIDO PROPAANOYL SN GLYCERO PHOSPHATID
L2 0 S STEAROYL DODECYLATE AMIDO PROPAANOYL SN GLYCERO PHOSPHATIDYLCH
L3 0 S STEAROYL DODECYLATE AMIDO PROPAANOYL GLYCERO PHOSPHATIDYLCHOLI
L4 0 S STEAROYL DODECYLATE PHOSPHATIDYLCHOLINE
L5 0 S STEAROYL DODECYLATE
L6 0 S STEAROYL PROPAANOYL SN GLYCERO PHOSPHATIDYLCHOLINE
L7 0 S STEAROYL (S) PROPAANOYL (S) GLYCERO (S) PHOSPHATIDYLCHOLINE
L8 7 S STEAROYL PHOSPHATIDYLCHOLINE

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, CANCERLIT, CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF, MEDLINE, NAPRALERT, NLDB, NUTRACEUT, PASCAL, PCTGEN, ...' ENTERED AT 15:50:02 ON 29 MAY 2003

FILE 'HOME' ENTERED AT 15:52:52 ON 29 MAY 2003

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT, CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF, MEDLINE, NAPRALERT, NLDB, NUTRACEUT, ...' ENTERED AT 15:53:04 ON 29 MAY 2003

FILE 'REGISTRY' ENTERED AT 16:00:45 ON 29 MAY 2003

L9 0 S SPHINGSINE/CN
L10 1 S SPHINGOSINE/CN

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BABS, BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHNO, CANCERLIT, CAPLUS, CBNB, CEN, CIN, CONFSCI, DGENE, DIOGENES, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, DRUGUPDATES, EMBAL, EMBASE, ESBIOBASE, FEDRIP, IFIPAT, ...' ENTERED AT 16:02:26 ON 29 MAY 2003

L11 21240 S STEAROYL
L12 5722 S PROPAANOYL
L13 422411 S GLYCEROL
L14 37687 S GLYCERO
L15 179691 S PHOSPHATIDYLCHOLINE

=> s l11 (s) l12 (s) l14 (s) l15
L16 2 L11 (S) L12 (S) L14 (S) L15

=> d l16 1-2 ibib, kwic

L16 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:208065 CAPLUS
DOCUMENT NUMBER: 134:242656
TITLE: Phospholipid prodrugs of anti-proliferative drugs
INVENTOR(S): Kozak, Alexander; Shapiro, Israel; Vinnikova, Marina;
Ershov, Leonid; Senderikhin, Alexander; Ayalon, Oran
PATENT ASSIGNEE(S): D-Pharm Limited, Israel
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	-----	-----	-----	-----

WO 2001019320

A2 20010322

WO 2000-IL562

20000913

WO 2001019320

A3 20010927

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2000073093

A5 20010417

AU 2000-73093

20000913

EP 1218013

A2 20020703

EP 2000-960946

20000913

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL

JP 2003514770

T2 20030422

JP 2001-522958

20000913

PRIORITY APPLN. INFO.:

IL 1999-131887

A 19990914

WO 2000-IL562

W 20000913

OTHER SOURCE(S): MARPAT 134:242656

AB The invention discloses prodrugs comprising anti-proliferative drugs covalently linked, via a bridging group, to a phospholipid moiety such that the active species is preferentially released, preferably by enzymic cleavage, at the required site of action. The invention further discloses pharmaceutical compns. comprising said prodrugs and the uses thereof for the treatment of diseases and disorders related to inflammatory, to degenerative or atrophic conditions, and to uncontrolled cell growth. A methotrexate deriv. 1-stearoyl-2-[3-(.alpha.-dodecylate-.gamma.-methotrexate-amido)-propanoyl]-sn-glycero-3-phosphatidylcholine was prep'd., and examd. for its inhibitory effect on human leukemia cell growth.

L16 ANSWER 2 OF 2 TOXCENTER COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:93159 TOXCENTER

COPYRIGHT: Copyright 2003 ACS

DOCUMENT NUMBER: CA13417242656W

TITLE: Phospholipid prodrugs of anti-proliferative drugs

AUTHOR(S): Kozak, Alexander; Shapiro, Israel; Vinnikova, Marina;
Ershov, Leonid; Senderikhin, Alexander; Ayalon, Oran

CORPORATE SOURCE: ASSIGNEE: D-Pharm Limited

PATENT INFORMATION: WO 2001019320 A2 22 Mar 2001

SOURCE: (2001) PCT Int. Appl., 51 pp.

CODEN: PIXXD2.

COUNTRY: ISRAEL

DOCUMENT TYPE: Patent

FILE SEGMENT: CAPLUS

OTHER SOURCE: CAPLUS 2001:208065

LANGUAGE: English

ENTRY DATE: Entered STN: 20011116

Last Updated on STN: 20020313

AB. . . of diseases and disorders related to inflammatory, to degenerative or atrophic conditions, and to uncontrolled cell growth. A methotrexate deriv. 1-stearoyl-2-[3-(.alpha.-dodecylate-.gamma.-methotrexate-amido)-propanoyl]-sn-glycero-3-

phosphatidylcholine was prep'd., and examd. for its inhibitory effect on human leukemia cell growth.